



Molecular Mechanisms of Periodontitis Development in Patients with Insulin Resistance and Ways of Its Treatment

1. **Komilova Adiba Zakirzhonovna**
2. **Hadzhimetov Abdugafur Akhatovich**
3. **Usmanova Shoira Ravshanbekovna**

Received 20th Aug 2023,
Accepted 21st Sep 2023,
Online 26th Oct 2023

¹ TASHKENT STATE DENTAL
INSTITUTE

Abstract: The analysis of modern data on the molecular mechanisms of the development and progression of insulin-dependent diabetes is presented. The leading role of HSP72 reduction in pancreatic cells and target organs for insulin in disorders of the structure of insulin molecules, its receptor perception, and mitochondrial functioning in DM2 is substantiated. New approaches to the treatment of DM2 have been discussed and proposed. Periodontitis in patients with diabetes mellitus has the same forms according to the clinical course, severity of manifestations, ontogenetic characteristics, and prevalence as in persons suffering from periodontitis, but not having diabetes mellitus. However, periodontitis in patients with diabetes mellitus, according to many authors, is poorly treatable and has an unfavorable prognosis.

Key words: insulin-dependent diabetes, insulin resistance, chronic generalized periodontitis.

Recently, the concept that chronic generalized periodontitis cannot be considered within the framework of a private pathology has been increasingly asserted. It has been established that this disease has associative relationships with various endocrine, immunological and other systemic disorders, which, in turn, may be the cause of other diseases, possibly secondary to periodontitis itself. One of the definitely associated pathologies is diabetes mellitus.

Currently, people in Uzbekistan suffer from diabetes mellitus, among which 90% are type II diabetes mellitus. Approximately one year after the detection of diabetes mellitus, 100% of patients have signs of chronic periodontitis with the prospect of complete loss of teeth [4]. On the other hand, according to the results of numerous studies of the problem, periodontitis is the most frequent complication of diabetes mellitus, which inevitably develops in almost every patient. At the same time, periodontitis is not only a complication itself, but also increases the risk of other complications, since it makes it difficult to conduct full-fledged diet therapy and correction of metabolic disorders inherent in diabetes, reduces the regenerative ability of periodontal tissues and sharply worsens the quality of life of diabetic patients [1, 5]. Important pathogenetic links in the development and progression of periodontal diseases in diabetes mellitus are considered microcirculatory disorders (diabetic microangiopathies), disorders in the immune system, acidosis. Disorders of microcirculation and immune cell functions can be both primary (under the influence of diabetes mellitus) and secondary (under the influence of the inflammatory process in periodontal disease).

The cause of inflammatory processes in periodontitis is xerostomia and secondary immunodeficiency. Periodontal diseases can be attributed to a group of small signs of diabetes mellitus [2, 6]. The authors of multicenter studies in the world tend to conclude that periodontopathogenic bacteria are one of the factors initiating the development of diabetes mellitus [1, 2, 7]. Conditions for a fairly stable relationship between periodontitis and type II diabetes mellitus arise due to the fact that diabetes mellitus is accompanied by a number of metabolic and immunological shifts, including oxidative stress, changes in the profile of cytokine production in the immune system, modulation of the receptor apparatus of cells, etc. [1, 3, 6, 8]. These shifts, combined with an increase in the glucose content in the oral fluid, create conditions for changes in the microbiota of the oral cavity, the appearance of periodontopathogenic species in its composition and, as a consequence, the development of a chronic recurrent inflammatory process in the periodontal with subsequent destruction of the alveolar bone and tooth loss [5, 9].

A significant role in the destruction of periodontal tissues in the presence of other risk factors and the formation of stable associations of early, intermediate and late colonizers is played by periodontopathogenic species of the 2nd order – *Fusobacterium nucleatum/periodonticum*, *Parvimonas micra*, *Prevotella intermedia*, *Porphyromonas endodontalis*, *Treponema denticola*, *Wolinella recta*. In parallel, such unfavorable factors as poor oral hygiene, occupational hazards, irrational diet, in particular, a decrease in the consumption of protein products and the absence of coarse food that reduces the load on the periodontal, smoking, unfavorable environmental factors are considered [1, 2, 5, 9].

Material and methods of research

In this regard, the aim of the study was to determine the features of the microbial composition of the biofilm of the dentoalveolar furrow in chronic periodontitis and the combination of chronic periodontitis with type II diabetes mellitus based on the use of modern molecular and metagenomic technologies. Patients and methods We conducted a comprehensive dental examination of 84 patients who applied to the dentist for treatment or prophylactic purposes, who met the criteria for inclusion in the study and filled out an informed consent. Group 1 consisted of 22 patients (11 men and 11 women aged 47-63 years), in whom type II diabetes was combined with the phenomena of chronic periodontitis.

They were diagnosed with periodontitis of moderate severity, confirmed by a detailed description of the dental status (Table. 1) and the results of PCR diagnostics for the detection of genetic markers of periodontopathogenic bacteria of the 1st and 2nd order. Group 2 included 30 patients (13 men and 17 women aged 42-60 years) who did not complain, and inflammatory periodontal diseases were detected in them when they applied for the treatment of caries and its complications. Based on clinical data, indicators of periodontal indices and the results of PCR diagnostics, they were diagnosed with "periodontitis of moderate severity", confirmed by a detailed description of the dental status and the results of PCR diagnostics. Control group 3 was formed by 22 individuals (9 men and 13 women aged 25-28 years) with a healthy (intact) periodontal disease and the absence of type II diabetes. This group includes only subjects with negative results of PCR diagnostics for the detection of genetic markers of periodontopathogenic bacteria of the 1st and 2nd order. The hygienic condition of patients in comparison groups 1 and 2 was satisfactory and comparable. According to the anamnesis, the following comorbid diseases were detected in patients of these groups: vegetative-vascular dystonia, symptomatic arterial hypertension, arterial hypertension. The prescription of periodontitis disease was 5-10 years. The previous periodontological treatment of patients of both groups included removal of dental deposits, local anti-inflammatory therapy and, according to indications, curettage of periodontal pockets. In the subjects of the control group 3 (without chronic periodontitis and type II diabetes), the hygienic condition of the gums was good, and the periodontal indices corresponded to normal values. The observation period for all subjects was 1.5 years. The material was taken from 4 sites in the area of the dentoalveolar furrow using sterile paper endodontic pins (No. 30), which were placed in a test tube with 0.2 ml of saline solution.

Research results and their discussion

As is known, many proteins cannot independently acquire their functionally active forms, as a result of which they tend to form distorted and inactive aggregates. The ability to transform and form aggregates has been proven for insulin molecules [5]. In cells, either special enzymes (foldases) or a group of auxiliary specialized proteins called chaperones contribute to maintaining the functionally correct structure of proteins. As it turned out, patients with DM2 had a reduced expression of chaperone HSP72, which clearly correlated with reduced insulin sensitivity [6]. It can be assumed that it is the deficiency of this chaperone in β -cells that does not allow the insulin molecules synthesized in the human pancreas to acquire the functionally necessary tertiary structure for interaction with the receptor, which is the most important cause of insulin resistance. 71 It was further found that not only in the pancreas, but also in the cells of peripheral organs consuming glucose (in skeletal muscles, liver, etc.), there is also a reduced expression of the HSP72 protein. It is important to note that a decrease in the formation of HSP72 was combined with increased phosphorylation of JNK – inflammatory cytokine, i.e., its activation. It is known that inflammation initiates the secretion of a number of inflammatory cytokines, such as tumor necrosis factor α (TNF- α) from macrophages and/or adipocytes, which leads to the activation of serine threonine kinases: c-jipamine-terminal kinase (JNK) and kinase inhibitor kB (IKK) in insulin-sensitive tissues. Under these conditions, the conformation of specific phosphatases is disrupted, which usually inhibit the activity of both JNK itself and the activity of proteins associated with JNK activation. [7]. Activated JNK and IKK are able to phosphorylate IRS-1(IRS-1) by Ser-307,

which makes this protein a poor substrate for the activated insulin receptor, leading to disruption of the activity of various signaling pathways, including those responsible for glucose uptake by the tissue. The importance of JNK and IKK in insulin resistance is emphasized by the fact that the genetic disruption of these pathways in mice provides protection against insulin resistance induced by obesity.

Literature

1. Sparrow, L. G., Macaulay, S. L. Insulin receptor complex and signaling by insulin // Hand Book of cell signaling (Eds. R.A. Bradshaw and E.A. Dennis) // Academic Press. – 2004. – 1. – P. 293–297.
2. Henquin, J. C. Triggering and amplifying pathways of regulation of insulin secretion by glucose // J. C. Henquin // Diabetes – 2000. – Vol. 49. – P. 1751–1760.
3. Mario Barbagallo, Ligia J. Dominguez Magnesium and type 2 diabetes // World J Diabetes 2015 August 25; 6 (10): 1152-1157.
4. Lwell, B. B. Mitochondrial dysfunction and tipe 2 diabetes / B. B. Lwell // Science. – 2005. – P. 384–387.
5. Некипелова, В. О. Агрегация инсулина в растворах / В. О. Некипелова // Биофарм. журн. 2009. – Т. 1. – № 3. – С. 3–9.
6. Kurucz, I. Decreased expression of heat shock protein 72 in skeletal muscle of patients with type 2 diabetes correlates with insulin resistance / I. Kurucz // Diabetes. – 2002. – P. 1102–1109.
7. Hirosumi, J. A central role for JNK in obesity and insulin resistance // J.Hirosumi // Nature. – 2002. – P. 333–336.
8. Karin Cucumel, Riad Domloge Skin-protecting dinucleotide examined // Journal Clinical Services. 2008 January; 25–28.
9. Гужова, И. В. Механизмы работы шаперона Hsp70 в нормальных клетках и при клеточной патологии. // Автореферат диссертации на соискание ученой степени доктора биологических наук по специальности 03.00.25 - гистология, цитология, клеточная биология. – СПб., 2004
10. Jason Chung, Anh-Khoi Nguyen, Darren C. Henstridge, Anna G. Holmes, M. H. Stanley Chan, Jose L. Mesa, Graeme I. Lancaster, Robert J. Southgate, Clinton R. Bruce, Stephen J. Duffy, Ibolya Horvath, Ruben Mestrl, Matthew J. Watt, Philip L. Hooper, Bronwyn A. Kingwell, Laszlo Vigh, Andrea Hevenertts, and Mark A. Febbraio HSP72 protects against obesity-induced insulin resistance // PNAS 2008. – Vol. 105. – No. 5 – P. 1739–1744.
11. Kavanagh, K. Tissue-specific regulation and expression of heat shock proteins in type 2 diabetic monkeys / K. Kavanagh, L. Zhang, JD. Wagner // Cell Stress Chaperones. – 2009. – Vol. 14. – P. 291–299.